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Reporting Adverse Reactions to Marketed Health Products

Guidance Document for Industry

Effective Date: May 23, 2018

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Forward

Guidance documents are meant to provide assistance on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with relevant sections of other applicable guidance documents.

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1 Introduction

1.1 Scope

This guidance document provides market authorization holders (MAHs) with assistance on how to comply with the *Food and Drugs Act*, the *Food and Drug Regulations*, and the *Natural Health Products Regulations* with respect to reporting adverse reactions (ARs) to marketed health products, but excluding blood and blood components and cells, tissues and organs (for further information on AR reporting for these products, see the Guidance Document: Blood Regulations and the Guidance Document for Cell, Tissue and Organ Establishments - Safety of Human Cells, Tissues and Organs for Transplantation). ARs for marketed health products within the scope of this guidance document are to be reported to the Canada Vigilance Program of the Marketed Health Products Directorate (MHPD) of Health Canada. This guidance document covers the collection of individual AR reports by MHPD for the following marketed health products:

- pharmaceutical drugs (which includes prescription and non-prescription pharmaceutical drugs);
- biologics as set out in Schedule D to the *Food and Drugs Act* (which include biotechnology products, vaccines and fractionated blood products);
- radiopharmaceutical drugs set out in Schedule C to the *Food and Drugs Act*; and
- natural health products as defined in Section 1 of the *Natural Health Products Regulations*.

In addition to the requirement for MAHs to submit AR reports in accordance with the *Food and Drugs Act*, the *Food and Drug Regulations* and the *Natural Health Products Regulations* (collectively these two sets of regulations are referred to hereafter as "the Regulations"), Health Canada has powers to request additional information on ARs as set out in the Regulations[1, 2, 3].

Note that drugs and natural health products authorized for clinical trials involving human subjects pursuant to Part C, Division 5 of the *Food and Drug Regulations*[4] and Part 4 of the *Natural Health Products Regulations*, respectively, are not within the scope of this guidance document. However, if a suspect product is marketed in Canada and is being tested as part of a study protocol authorised by Health Canada [i.e., by means of a clinical trial application (CTA)], the MAH must report spontaneous and solicited ARs occurring outside of the study protocol (CTA) to MHPD in accordance with Divisions 1 and 8 of the *Food and Drug Regulations* or Section 24 of the *Natural Health Products Regulations* unless the MAH is also the sponsor of the study.

This guidance document does not cover the preparation and collection of summary reports, such as annual summary reports (ASR) and issue-related summary reports. For assistance on how to comply with the *Food and Drug Regulations* and the *Natural Health Products Regulations* with respect to annual and issue-related summary reports, MAHs should contact MHPD (see Appendix 4 for contact information).

For Adverse Reaction Reporting outside the scope of this document, see Appendix 5 provides further details on these other reporting programs.

1.2 Adverse Reaction Reporting by Market Authorization Holders

Every MAH is required to report serious ARs known to them involving their marketed health products in accordance with the requirements of the *Food and Drugs Act* and the *Regulations*. The success of Health Canada's AR reporting system depends on the quality, completeness, accuracy, and timeliness of the information submitted. Reporting of ARs and the monitoring thereof remain a viable means of identifying previously unrecognized, rare or

serious ARs. This may result in changing product safety information, facilitating decisions on regulatory actions such as withdrawal of a product from the Canadian market, contributing to international data regarding risks and effectiveness of health products, and imparting health product safety knowledge that benefits all Canadians.

In facilitating reporting of ARs by MAHs, Health Canada has harmonized to the greatest extent possible the recommendations in the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance documents: *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*[5] (ICH E2A), *Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports*[6] (ICH E2B(R2)), *Periodic Benefit-Risk Evaluation Report*[7] (ICH E2C(R2)), and *Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting*[8] (ICH E2D), *Pharmacovigilance Planning*[9] (ICH E2E), and the *Report of the Council for International Organizations of Medical Sciences (CIOMS) V Working Group: Current Challenges in Pharmacovigilance: Pragmatic Approaches*[10].

1.3 Adverse Reactions

This guidance document applies to adverse reactions (ARs) rather than adverse events (AEs). ARs to marketed health products covered by this document may be generated from unsolicited and solicited reports.

An AR, in contrast to an AE, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. The definition of adverse reaction[1, 11] (see Appendix 1) implies that there is a suspected relatedness to the administered health product. Health professionals and consumers report adverse reactions because of their suspicion of the relatedness of an adverse event to a health product. The description of experiences in these reports should therefore be considered adverse reactions. Reportable ARs also include those suspected of being the result of drug interactions (e.g., drug-drug interactions, drug-natural health product interactions, drug-food interactions).

An adverse event, as defined in ICH E2D[8], means any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

1.4 Serious Adverse Reaction Reports

A serious adverse reaction is defined in the Regulations as a noxious and unintended response to a drug or natural health product that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.

Medical and scientific judgement by a qualified health professional should be exercised in deciding whether expedited reporting is appropriate in other situations, such as medically important events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition from the Regulations. Health Canada asks that these cases be reported on an expedited basis as well.
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The seriousness criterion should not be downgraded from serious to non-serious if the receiver (e.g., MAH) disagrees with the seriousness reported by the reporter.

1.5 Unexpected Adverse Reaction Reports

An AR is considered unexpected when its nature (i.e., specificity or outcome), severity or frequency is either not identified, or is not consistent with the terms or description used in the product labelling. In cases where the MAH is uncertain whether an AR is expected or unexpected, the AR should be treated as unexpected.

For both domestic and foreign reports, expectedness is determined from relevant Canadian labelling such as the product monograph, labelling standards, information approved for market authorization, or the product label.

For cases that involve a fatal outcome, AR reports should be considered unexpected unless the product labelling specifically states that the AR may be associated with a fatal outcome.

Class ARs should not automatically be considered expected for the subject health product. Class ARs should be considered expected only if described as specifically occurring with the product in the product labelling as illustrated in the following examples:

- "As with other health products of this class, the following undesirable effect occurs with Product X."
- "Health products of this class, including Product X, can cause..."

If the AR has not been documented with Product X, statements such as the following are likely to appear in the product labelling:

- "Other health products of this class are reported to cause..."
- "Health products of this class are reported to cause..., but no reports have been received to date with Product X."

In these situations, the AR should not be considered as expected for Product X.

1.6 Regulations Pertaining to Adverse Reaction Reporting

The sections of the applicable regulations that set out the AR reporting requirements are listed below.

Food and Drug Regulations

- *Prohibition (C.01.016)*
- *Serious Adverse Drug Reaction Reporting (C.01.017)*
- *Annual Summary Report and Case Reports (C.01.018)*
- *Issue-related Summary Report (C.01.019)*
- *Maintenance of Records (C.01.020)*
- *New Drugs (C.08.007, C.08.008)*

Natural Health Products Regulations

- *Reaction Reporting (24)*

2 General Procedures for Expedited Adverse Reaction Reporting

Every MAH should put into place written procedures for the receipt, evaluation, and reporting of ARs.

Reporting of ARs electronically is the preferred and most reliable method for MAHs to comply with regulatory timelines. As soon as they are capable of doing so, MAHs should enrol with Health Canada as trading partners to submit individual case safety reports (ICSRs) electronically in accordance with the technical requirements and business (validation) rules set out in a document which is available on request via Health Canada's Trading Partner Management Office (TPMO), see Appendix 4 for contact information. Reporting of ARs electronically significantly reduces the amount of time and effort involved in the reporting process.

MAHs that do not yet meet the technical requirements to submit ARs electronically, as defined in the aforementioned instruction document, may continue to send AR reports to MHPD by fax or by mail (see Appendix 4 for contact information). The preferred reporting format for AR reporting by MAHs via fax and mail is as follows:

- for drugs, the Council for International Organizations of Medical Sciences (CIOMS) Form I[13]
- for natural health products, the Mandatory Adverse Reaction Reporting Form for Industry[14]

For more information on the expectations with respect to pharmacovigilance systems, MAHs should consult Health Canada's Good Pharmacovigilance Practices (GVP) Guidelines GUI-0102[15].

2.1 Domestic and Foreign Adverse Reaction Reports

For drugs, MAHs must submit domestic and foreign AR reports to MHPD pursuant to Part C, Division 1 (C.01.016, C.01.017) and for new drugs must submit reports of unusual failure in efficacy pursuant to Part C, Division 8 (C.08.007, C.08.008) of the *Food and Drug Regulations* once their drugs are available for sale in Canada. These reporting obligations (see sections 2.1.1 and 2.1.2) for MAHs commence when the MAH sells a drug, which can occur for example when a MAH offers a drug for sale, exposes a drug for sale or has a drug in its possession for sale and distribution.

For natural health products, MAHs must submit domestic and foreign AR reports to MHPD as set out in Section 24 of the *Natural Health Products Regulations* once their health product is licensed to be marketed in Canada.

To facilitate the processing of AR reports, the MAH should indicate if the report is domestic or foreign by clearly indicating the country where the reaction occurred.

The regulatory reporting time clock is considered to start on the day when the MAH (the entity that holds the Drug Identification Number (DIN), Natural Product Number (NPN), or Homeopathic Medicine Number (DIN-HM)) first has all of the information that satisfies the minimum criteria for an AR report (see Section 3.1). This date should be considered day 0. If the collection of ARs is performed by a separate entity through a contractual agreement (e.g. co-marketer or third-party company), the day on which the contracted person or organization receives the ARs should be considered day 0. Please refer to section 3.6 for more information on contractual agreements.

2.1.1 Domestic Adverse Reaction Reports

AR reports concerning reactions occurring in Canada to a product that is marketed in Canada are considered "domestic" AR reports.

In order to report in accordance with the Regulations, it is sufficient that each MAH report to MHPD in an expedited fashion (within 15 calendar days of receiving the relevant information) the following domestic reports:

- **serious** ARs (expected and unexpected)
- unusual failure in efficacy reports for new drugs (see Appendix 1 for New Drug definition).

Inquiries regarding new drug status for health products marketed in Canada should be referred to the appropriate Directorate (i.e., Biologics and Genetic Therapies Directorate or Therapeutic Products Directorate).

2.1.2 Foreign Adverse Reaction Reports

Foreign AR reports are those concerning reactions occurring outside Canada to a product that is marketed in Canada.

In order to report in accordance with the Regulations, it is sufficient that each MAH report to MHPD in an expedited fashion (within 15 calendar days of receiving the relevant information) the following foreign reports:

- **serious unexpected** ARs.

All foreign serious unexpected AR reports involving the MAH's foreign products with the same combination of active ingredients irrespective of variations in the formulation, dosage form, strength, route of administration, or indication, that is also marketed in Canada must be reported to MHPD in accordance with the Regulations (e.g., a MAH that sells a marketed health product in Canada with active ingredients X, Y, and Z, must report all foreign serious unexpected AR reports involving their foreign products with the same combination of active ingredients X, Y, Z).

If the product source, brand, or trade name is not specified, the MAH should assume that it was its own product, although the report should indicate that the specific brand was not identified.

2.1.2.1 Canada's Access to Medicines Regime

In response to public health problems afflicting many developing and least-developed countries, Canada passed an Act to amend the *Patent Act* and the *Food and Drugs Act* (*The Jean Chrétien Pledge to Africa*). The Act, which came into force on May 14, 2005, creates a legislative framework that enables manufacturers to obtain an authorization (i.e., compulsory licence) allowing them to make, construct and use a patented invention solely for the purpose of exporting a pharmaceutical product to eligible importing countries. The provisions of the Act are now incorporated in the *Patent Act* and the *Food and Drugs Act*, following their amendment after the coming into force of the Act.

Compulsory licence holders are subject to the requirements for reporting foreign adverse reactions to health products sold under Canada's Access to Medicines Regime (CAMR). Compulsory licence holders

submitting these reports to MHPD are requested to specify the following on the cover sheet: FOREIGN ADVERSE REACTION, CANADA's ACCESS TO MEDICINES REGIME.

2.2 Other Adverse Reaction Report Types

Sections 2.2.1 to 2.2.3 applies to all products that fall under the FDR and NHPR:

2.2.1 Overdose, Medication Error or Occupational Exposure

Cases of overdose, medication error or occupational exposure associated with serious ARs are subject to expedited reporting in accordance with the Regulations. They should be routinely followed up to ensure that the information is as complete as possible with regard to symptoms, treatment, outcome, and context of occurrence (e.g., error in prescription, administration, dispensing, dosage, etc.). The MAH should collect any available information on these cases related to its products.

2.2.2 Pregnancy Exposure

MAHs are expected to follow up all pregnancy reports from health professionals and consumers where the embryo/foetus could have been exposed to one of its health products. For consumer reports, it is appropriate to seek permission to only follow up with the health professional. The MAH must apply all principles outlined in this guidance document and the Regulations pertaining to reporting requirements, including determination of seriousness and minimal criteria for submitting an AR report. Reports of pregnancy exposure with no associated adverse reactions should not be reported as ARs. When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering whether a foetus could have been exposed (e.g., if health products taken before the gestational period should be considered). Care should be taken when reporting ARs related to the embryo/foetus that the patient and the parent/child relationship are accurately identified in the report, and that the AR information is attributed to the correct patient. For example, if an AR occurs in both the parent and foetus, then 2 separate AR reports should be submitted, if the reporting requirements are met as indicated in the E2B (R2) Guidance document, section B.1.

2.2.3 Discontinued Products

In accordance with the Regulations, the MAH must report any AR information received prior to the discontinuation of sale in Canada. Although the MAH is not obliged to report any new cases of adverse reactions received following the product's discontinuation, Health Canada strongly encourages the reporting of all serious adverse reactions and may request the provision of this information. If a serious AR was known to the MAH before the discontinuation of sale, they must still report as per the expedited reporting requirements even if the end of the 15-day reporting timeframe as required by the Regulations is after the date on which sales were discontinued. Follow-up information for cases known to the MAH prior to the discontinuation of sale should be reported to MHPD in accordance with the Regulations, and should be sought as part of the follow-up practices described under Section 3.4.

When expired and unexpired lots of a discontinued product continue to be available in pharmacies, the MAH is still under obligation to report ARs to MHPD if this information was received by the MAH prior to the discontinuance. As mentioned above, Health Canada may still request the MAH to provide information that it receives following the discontinuation of sales.

2.2.4 Unusual Failure in Efficacy (only applies to new drugs)

The MAH must report an unusual failure in efficacy of a new drug in accordance with Part C, Division 8 of the *Food and Drug Regulations*. For **new drugs marketed in Canada**, domestic reports of unusual failure in efficacy must be reported to MHPD within 15 calendar days of the receipt of information by the MAH. Inquiries regarding new drug status for health products marketed in Canada should be referred to the appropriate Directorate (i.e., Biologics and Genetic Therapies Directorate or Therapeutic Products Directorate).

The underlying principle is that if a health product fails to produce the expected intended effect, there may be an adverse outcome for the patient, including an exacerbation of the condition for which the health product is being used. An AR that is determined to be an unusual failure in efficacy should be reported to MHPD in an expedited fashion regardless of whether the reaction itself is imminently serious. Clinical judgement should be exercised by a qualified health professional from the MAH to determine if the problem reported is related to the product itself, rather than one of treatment selection or disease progression since health products cannot be expected to be effective in 100% of the patients. One example of unusual failure in efficacy is a previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription. Another example of a case that should be reported on an expedited basis is a life-threatening infection where the failure in efficacy seems to be due to the development of a newly resistant strain of bacterium previously regarded as susceptible.

In cases where the MAH is uncertain whether an AR should be considered as a report of unusual failure in efficacy, the AR should be treated as such and submitted to MHPD accordingly.

3 Good Case Management Practices

3.1 Minimum Criteria for an Adverse Reaction Report

Complete information for the final description and evaluation of an AR report may not be available within the time frame required for reporting. Nevertheless, for regulatory purposes, AR reports must be submitted within the prescribed time, as long as the following minimum criteria are met:

(a) An identifiable reporter (source)
(b) An identifiable patient
(c) A suspect product
(d) An adverse reaction.

Ideally, more comprehensive information would be available on all cases from the outset, but in practice MAHs will often have to follow up with the reporter after initially submitting the report to seek additional information. Follow-up AR reports should be clearly labelled as such (see section 3.4). The MAH is expected to exercise due diligence to collect any key data elements (see Section 3.8) that are lacking at the time of initially submitting the report. The MAH should provide all information that is available and relevant in the initial AR report and not just that which satisfies the minimum criteria. See section 3.8 for a list of key data elements which enhance report quality.

It is important that at the time of the original report, sufficient details about the patient and reporter be collected and retained to enable follow-up in accordance with the collection, use and disclosure provisions of the *Personal Information Protection and Electronic Documents Act* or equivalent provincial privacy legislation.

3.2 Assessing Patient and Reporter Identifiability

Patient and reporter identifiability is important to avoid case duplication, and facilitate follow-up of appropriate cases. The term "identifiable" in this context refers to the verification of the existence of a patient and a reporter. AR cases without specific identifiers (e.g., reporter name or patient gender) may meet the first two reporting criteria outlined in section 3.1, however, follow-up information should be actively sought and submitted as it becomes available. All parties submitting case information or approached for case information should be identifiable: not only the initial reporter (the initial contact for the case), but also others supplying information. In addition, in the event of second-hand reports, every reasonable effort should be made to verify the existence of an identifiable patient and reporter.

One or more of the following should automatically qualify a patient as identifiable: age or age category (e.g., adolescent, adult, elderly), gender, patient identification number, or reference to "a patient". In the absence of qualifying descriptors (e.g., age, gender), a report referring to a number of patients should not be regarded as a case until the minimum four criteria for case reporting are met. For example, "a few patients experienced" should be followed up for patient-identifiable information before reporting to MHPD. The four minimum criteria must be met for each reported patient and an individual report should be submitted for each identifiable patient. The regulatory time clock (i.e. day 0) does not begin until all four minimum criteria are met, e.g. once "a few patients" are identified as patients X, Y, and Z, and the other three criteria are met.

Provide as many patient identifiers in appropriate structured fields when reporting. For instance, do not simply include "female" as a patient identifier when it is known that the patient was a 29 year old female. Inclusion solely in the narrative field is not sufficient.

3.3 The Role of Narratives

The objective of the narrative is to summarize all relevant clinical and related information, including patient characteristics, therapy dates, medical history, clinical course of the event(s), diagnosis, and AR(s) including the outcome, laboratory evidence (including normal ranges), and any other information that supports or refutes an AR (e.g., rechallenge information). The narrative should serve as a comprehensive, stand-alone "medical story". Care should be taken by the MAH to ensure that the information in the narrative (e.g., patient identifiers, ARs, indication, and medical conditions) is accurately captured in the appropriate data fields.

Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units. Key information from supplementary records including summarized relevant autopsy or post-mortem findings should be included in the report, and their availability should be mentioned in the narrative and supplied on request. Clinical judgement should be exercised by a qualified health professional from the MAH to determine what information should be submitted. Personal identifiers should only be submitted in accordance with the collection, use and disclosure provisions of the *Personal Information Protection and Electronic Documents Act* or equivalent provincial privacy legislation.

3.4 Follow-up Information

Follow-up information should be actively sought and significant new information must be submitted by the MAH as it becomes available for appropriate amendment to the database and files in MHPD. Follow-up AR reports should be appropriately linked to the initial report. For reporting and case management purposes, the initial report is considered to be the first report that is sent to MHPD. Follow-up information should be clearly identified within the report, and should be updated in the narrative sequentially by the date it was received by the MAH. Corresponding data fields should be updated accordingly. The MAH should ensure that the MAH received date of any follow-up information does not precede the latest received date of the previous report version.

When additional medically significant information is received for a previously reported case, the reporting time clock (see Section 2.1) is considered to begin again for submission of the follow-up report. Significant follow-up information received by the MAH for serious domestic ARs and serious unexpected foreign ARs must be reported to MHPD within 15 calendar days. For the purpose of reporting, significant follow-up information relates to, for example, new suspected adverse reaction(s), additional or changed suspect product, a change in the causality assessment and any new or updated information on the case that impacts its medical interpretation. Therefore, the identification of significant new information requiring expedited reporting always necessitates the qualified health professional's medical judgement. Routine tests conducted independently of the adverse reaction(s), or follow-up results for a test previously reported may not require expedited reporting unless the results are deemed significant (e.g., impact the medical interpretation of the case) by the qualified health professional from the MAH.

In addition, a case initially classified as a non-expedited report, would qualify for expedited reporting upon receipt of follow-up information that indicates the case should be re-classified (e.g., from non-serious to serious). In the reverse scenario, where an initially serious case is re-classified as non-serious, this information is still subject to the 15-day expedited reporting timeline; thereafter for re-classified cases as non-serious, additional information is not subject to 15-day timelines, in so long as the case remains non-serious.

In any scheme to optimize the value of follow-up, the first consideration should be prioritization of case reports by importance. The priority for follow-up should be as follows: cases which are (1) serious and unexpected, (2) serious and expected, and (3) non-serious and unexpected. Although non-serious and unexpected cases are not expedited, MAHs are encouraged to pursue follow-up information on these reports. In addition, cases of "special interest" also

deserve extra attention as high priority (e.g., ARs under enhanced or active surveillance at the request of Health Canada), as well as any cases that might lead to a labelling change decision.

Follow-up information should be obtained, via a telephone call and/or site visit and/or a written request. The MAH should ask specific questions it would like to have answered. Follow-up methods should be tailored towards optimizing the collection of missing information. If appropriate, written confirmation of details given verbally should be obtained. All attempts to obtain follow-up information (whether or not successful) should be documented as part of the case file, particularly on the serious cases. The number of follow-up attempts along with the date and time of each should be documented to reflect sufficient diligence.

To facilitate the capture of clinically relevant and complete information, use of a targeted questionnaire/specific form is encouraged, preferably at the time of the initial report. Ideally, qualified health professionals should be involved in the collection and the direct follow-up of reported cases. For serious ARs, it is important to continue follow-up and report new information until the outcome has been established or the condition is stabilized. The amount of time devoted to follow up such cases is a matter of the qualified health professional's judgement.

3.5 Evaluation and Coding of Adverse Reaction Reports

The purpose of careful medical review by qualified health professionals is to ensure correct interpretation of medical information. Preferably, information about the case should be collected from the health professionals who are directly involved in the patient's care. Regardless of the source of an AR report, the MAH should carefully review the report for the quality and completeness of the medical information. The review should include, but is not limited to, the following considerations:

- Has a diagnosis been assigned?
- Have the relevant diagnostic procedures been performed?
- Were alternative causes of the reaction(s) considered?
- What additional information is needed?

The Medical Dictionary for Regulatory Activities (MedDRA), an ICH initiative (ICH M1), is an internationally accepted, clinically validated medical terminology developed to share regulatory information about medical products used by humans. MedDRA provides a set of terms which consistently categorizes medical information and is meant to standardize the terminology through which medical regulatory information is classified, stored, retrieved, presented and communicated.

In order to avoid loss or distortion of communicated information, it is recommended that MedDRA be used as a standard for the coding of medical information in AR reports. MedDRA coding should be applied to all medical information (e.g. ARs, medical history, and indications) whenever possible. For trading partners who are submitting ICSRs electronically to MHPD, exclusive use of the current version of MedDRA is required.
When using the MedDRA terminology for the coding of AR reports, two supporting ICH-endorsed guides are available for MedDRA users:

- MedDRA Term Selection: Points to Consider (MTS:PTC)[16] document for accurate and consistent term selection, and
- MedDRA Data Retrieval: Points to Consider (MDR:PTC)[17] for consistent use of MedDRA for data analysis/output and presentation of medically meaningful review and analysis of clinical data.

The MedDRA Points to Consider documents aid in standardising the use of MedDRA between various users. Term selection methods and quality assurance procedures for coding adverse reaction reports should be documented in MAH-specific coding guidelines which should be based on, and not in conflict with, the MTS:PTC. In some cases, where there is more than one option for selecting terms, the MTS:PTC document identifies a preferred option. A MAH should be consistent in the option that they chose, and should document their selected option in their MAH-specific coding guidelines.

Every effort should be made to use AR terms consistently and in accordance with recommended standards for diagnosis. The report should include the verbatim term as used by the reporter, or an accurate translation of it if provided in a language other than English or French. Any MAH personnel receiving reports should provide an unbiased and unfiltered report of the information from the reporter. While the report recipient is encouraged to actively query the reporter to elicit the most complete account possible, inferences and imputations should be avoided in report submission. However, clearly identified evaluations by the MAH are considered appropriate.

When a case is reported by a consumer, his/her description of the event should be retained, although confirmatory or additional information from any relevant qualified health professionals should also be sought and included as part of the follow-up practices described under Section 3.4.

As described in Sections 1.4, 4.1.1, and 4.2, where the receiver (e.g., MAH) disagrees with the reporter's seriousness criterion or suspicion of a causal relationship between the suspected health product and the reported adverse reaction, these should not be downgraded by the MAH. The opinions of both the reporter and the MAH should be recorded in the AR report.

3.6 Contractual Agreements

The marketing of many health products increasingly takes place through contractual agreements between two or more companies, which may market the same product in the same or different countries or regions. Arrangements vary considerably with respect to inter-MAH communication and regulatory responsibilities. Therefore, it is essential that explicit licensing or contractual agreements specify the processes by which an exchange of safety information, including timelines and regulatory reporting responsibilities, are taking place. Pharmacovigilance personnel should be involved in the development of any agreements from the beginning. Processes should be in place to avoid duplicate reporting to the regulatory authority (e.g., assigning the responsibility to one MAH for literature screening).

Whatever the nature of the arrangement, the MAH is ultimately responsible for regulatory reporting. Therefore, every effort must be made between the contracting partners to minimize the data exchange period so as to promote compliance with MAH reporting responsibilities. For MAHs that have a contractual agreement for the initial collection of ARs, the regulatory timeclock begins when the contracted person or organization first receives the AR and the four minimum criteria for reportability are met.

3.7 Records to be Held for Auditing (C.01.020)

The *Food and Drug Regulations* require that records of the AR case reports and summary reports, be maintained. For drugs, the MAH must retain records for 25 years after the day on which they were created. It is also recommended that these records be easily accessible within 72 hours.

For natural health products, records of the AR case reports and summary reports should be maintained to permit audit or submission on request. A minimum 25 year retention period is recommended from the date the record was created. It is also recommended that these records be easily accessible within 72 hours.

3.8 Key Data Elements

The following is a list of key data elements that enhance the quality of an AR report. The MAH is expected to exercise due diligence in obtaining information on as many listed items as are pertinent to the case.

1. **Patient Details**
   - Unique identifier (to readily locate the case for follow-up purposes; do not use the patient's full name)
   - Gender
   - Age, age category (e.g., adolescent, adult, elderly)
   - Height and weight
   - Pre-existing conditions
   - Medical history
   - Relevant family history

2. **Suspected Health Product(s)**
   - Brand name as reported [the brand name is the name assigned by the MAH, used to distinguish the health product, and under which the health product is sold or advertised, and includes any name extensions or modifiers (prefix or suffix)]
   - Canadian authorization numbers such as a Drug Identification Number (DIN); Homeopathic Medicine Number (DIN-HM) and Natural Product Number (NPN) which appear on the label
   - Common Name such as the International Nonpropriety Name (INN)
   - For natural health products, it is important to include the Latin binomial, author reference, family (genus and species), type of extract (e.g., aqueous versus alcoholic, including percent of solvent), part of the plant used (in the case of an herbal product), ingredients and quantity of each (for homeopathic products, potency of each ingredient). If a particular ingredient in a combination is suspected, this should also be identified.
   - Batch/lot number
   - Indication(s) for which suspect health product was prescribed or tested, or indicate if unknown
   - Dosage form and strength
   - Daily dose (specify units, e.g., mg, ml, mg/kg) and regimen
   - Route of administration; unknown route of administration should be indicated as such
   - Starting date and time
   - Stopping date and time, and duration of treatment
   - For vaccines, indicate the number of previous doses of each vaccine. For example, if the event occurred after a series of several vaccinations (e.g., 3 doses of hepatitis B vaccine) give details of prior immunizations in the narrative

3. **Concomitant and Other Treatment(s)**
   The same information as in item 2 should be provided for the following:
   - Concomitant health products (including non-prescription, over-the-counter medicinal products, natural health products, dietary supplements, complementary and alternative therapies, etc.)
   - Health products used in the treatment of the AR.

- Any other health products being used at the time of the AR, including medical devices

4. **Details of AR(s)**
   - Full description of reaction(s), including body site and severity
   - The criterion (or criteria) for regarding the report as serious if reported as such
   - Description of the reported signs and symptoms
   - Specific diagnosis for the reaction
   - Onset date (and time) of reaction
   - Stop date (and time) or duration of reaction
   - Dechallenge and rechallenge information; unknown action taken should be indicated as such
   - Relevant diagnostic test results and laboratory data
   - Setting (e.g., hospital, out-patient clinic, home, nursing home)
   - Outcome (recovery and any sequelae)
   - For a fatal outcome, stated cause of death
   - Relevant autopsy or post-mortem findings
   - Relatedness of product to reaction(s)/event(s)

5. **Reporter Details**
   - Reporter type (consumer, health professional, etc.)
   - Profession (specialty)

The following is a list of the administrative and MAH details that should always be included with the report:

- Source of report (e.g., clinical trial, literature, spontaneous, regulatory authority)
- Date the event report was first received by MAH
- Country in which the reaction occurred
- Type (initial or follow-up) and sequence (first, second, etc.) of case information reported to Health Canada
- Name and address of MAH
- Name, address, electronic mail address, telephone number, and facsimile number of contact person of MAH
- MAH's identification number for the case (the same number should be used for the initial and follow-up reports on the same case).

4 Adverse Reaction Reports by Source

4.1 Unsolicited Reports

An unsolicited report is a spontaneous report which is defined by the ICH as an unsolicited communication by a health professional or consumer to a MAH, regulatory authority (i.e., Health Canada) or other organization that describes one or more ARs in a patient who was given one or more health products and that is not derived from a study or any organized data collection scheme.

4.1.1 Consumer Reports

Consumer AR reports should be handled as spontaneous reports irrespective of any subsequent "medical confirmation". Emphasis should be placed on the quality of the report and not on its source.

If a MAH receives a report from a consumer, the MAH should encourage the patient to report the reaction through their health professional or permission should be sought to contact the consumer's health professional. In addition, the MAH should attempt to obtain as much information as possible from the patient. The description of the experiences in these reports should therefore be considered adverse reactions.

A valid case of suspected adverse reaction initially submitted by a consumer cannot be downgraded to a report of non-related adverse event if the contacted health professional (e.g., nominated by the consumer for follow-up information) disagrees with the consumer's suspicion. In this situation, the opinions of both the consumer and the health professional should be included in the AR report.

If the minimum reporting criteria are met and the report is considered relevant by a qualified health professional from the MAH, the case is considered "reportable" and must be forwarded to MHPD in accordance with the Regulations. Even if reports received from consumers do not qualify for expedited regulatory reporting, the cases should be retained as they are applicable to the annual summary reporting requirements in the Regulations.

4.1.2 Reports Submitted to the Canada Vigilance Program by consumers or health professionals

If a MAH becomes aware of a report that has been submitted by a health professional or consumer to the Canada Vigilance Program, the MAH must also submit the report to MHPD via the Canada Vigilance Program and quote the Canada Vigilance Adverse Reaction Report Number (AER) number in accordance with the Regulations and should clearly indicate that the report was also sent to a Canada Vigilance Program. Please note that MAHs should submit reports to MHPD Canada Vigilance Program, coordinates listed in Appendix 4, and not the Canada Vigilance Regional Offices.

4.1.3 Scientific Literature Reports

Every MAH is expected to screen the worldwide scientific literature on a regular basis by accessing widely used systematic literature reviews or reference databases. It is recommended that the frequency of the literature searches be at least every two weeks. A qualified health professional from the MAH should use their clinical judgement to determine the appropriate frequency of literature searches based on the health product marketed by the MAH. Cases of ARs from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, might qualify for expedited reporting. An individual report with relevant medical information must be provided for each identifiable patient. The publication reference(s) should be

given as the report source. Additionally, the MAH is expected to provide the article to MHPD upon request. All MAH offices (e.g. global and regional offices) should be aware of publications in their local journals and to bring them to the attention of the MAH safety department as appropriate.

The regulatory reporting time clock starts as soon as the MAH has knowledge that the case meets minimum criteria for reportability.

For foreign literature reports, all foreign serious unexpected ARs involving the MAH's foreign products with the same combination of active ingredients irrespective of variations in the formulation, dosage form, strength, route of administration, or indication, that is also marketed in Canada must be reported to MHPD in accordance with the Regulations (see Section 2.1.2).

If the product source, brand, or trade name is not specified, the MAH should assume that it was its own product, although the report should indicate that the specific brand was not identified.

If multiple products are mentioned in the article, a report should be submitted only by the MAH whose product is suspected. The suspect product(s) is/are those identified as such by the article's author.

4.1.4 Stimulated Reports

Stimulated reports are those that may have been motivated, prompted or induced and can occur in certain situations, such as notification by a Health Professional Communication (HPC), Health Canada-issued Public Advisory and/or Public Communication (PC), literature report, publication in the press, or questioning of health professionals by MAH representatives. These reports should be considered unsolicited in nature and must be reported to MHPD in accordance with the Regulations.

4.1.5 Reports via the Internet

MAHs should regularly screen websites under their management or responsibility for potential AR case reports. MAHs are not expected to screen external websites for AR information. However, if a MAH becomes aware of an AR on a website that it does not manage, the MAH should review the case and determine whether it should be reported.

MAHs should consider utilising their websites to facilitate AR data collection, e.g., by providing AR forms for reporting or by providing appropriate contact details for direct communication.

Cases from the Internet should be handled as unsolicited reports. For the determination of reportability, the same minimum criteria (i.e., identifiable reporter, identifiable patient, suspect product and AR) should be applied as for cases provided via other ways. If the minimum reporting criteria are met and the report is considered relevant by a qualified health professional from the MAH, the case is considered "reportable" and must be forwarded to the MHPD in accordance with the Regulations.

4.1.6 Other Unsolicited Reports

If a MAH becomes aware of a case report from non-medical sources (e.g., the lay press or other media), it should be handled as an unsolicited report. For the determination of reportability, the same minimum criteria (i.e., identifiable reporter, identifiable patient, suspect product and AR) should apply as for other reports.

4.2 Solicited Reports

Solicited reports are defined by the ICH as those derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or health professionals, or information gathering on efficacy or patient compliance. AR reports obtained from any of these sources should not be considered unsolicited. Such reports are regarded as solicited in nature and one cannot infer implied causality, the convention for spontaneous reports. Solicited reports should also not be confused with stimulated reports (see Section 4.1.4).

For the purposes of AR reporting, solicited reports should only be submitted if there is a reasonable possibility that the health product caused the AR as determined by a qualified health professional of the MAH. A "reasonable possibility" means that the relationship cannot be ruled out. For example, using the World Health Organization criteria for causality applicable to AR reporting, any case reports that fall within the criteria of Certain, Probable, Possible, or Unlikely (see Appendix 6) must be reported to MHPD. In any case where an underlying illness or another health product may have contributed to the adverse event, the report should still be considered an AR, as the causality cannot be ruled out.

For solicited reports, where the receiver (e.g., MAH) disagrees with the reasonable possibility of causal relationship between the suspected health product and the adverse reaction expressed by the reporter, the case should not be downgraded to a report of non-related adverse event. The opinions of both the reporter and the MAH should be recorded in the AR report.

4.2.1 Patient Support and Disease Management Programs

A number of solicited reports are generated through the increasing use of methods to encourage contact between consumers and the MAH, such as through marketing programs as part of another patient support and disease management program used by MAH. Examples of these programs include, but are not limited to, telephone services for patients to obtain direct advice, nurse-initiated calls for medicine compliance management, surveys collecting other patient data, and establishment of large patient registries. These reports are clearly not generated in the usual spontaneous manner that is the premise upon which unsolicited reporting systems are based; they are usually obtained incidentally to the main purpose of the program. Reports generated through these programs are considered solicited reports and are reportable in accordance with the Regulations. Follow-up information should only be submitted on an expedited basis if it is considered to be medically significant by the qualified health professional from the MAH (see Section 3.4).

4.2.2 Reports from Studies

For studies, this section of the guidance document refers to the MAH's post-market AR reporting requirements for marketed health products, Division 1 (C.01.016 and C.01.017) and Division 8 (C.08.007(h) and C.08.008(c)) of the *Food and Drug Regulations* and Section 24 of the *Natural Health Products Regulations*.

MAHs are subject to AR reporting for health products used in studies where the MAH is the sponsor of the study, in accordance with the requirements listed in Part C, Division 5 of the *Food and Drug Regulations*, or Part 4 of the *Natural Health Products Regulations*. These requirements are not within the scope of this guidance document (see Appendix 5 for program information).

4.2.2.1 Market Authorization Holder Sponsored Studies

Studies subject to post-market AR reporting requirements (e.g., phase IV studies) should be monitored in a way that ensures that all serious domestic ARs, serious unexpected foreign ARs and reports of domestic unusual failure in efficacy for new drugs are reported to the MAH by the investigator(s) so that the MAH can provide such reports to MHPD within the 15-day period specified in the Regulations.

Investigators should be provided with the definition of what constitutes a serious AR for reporting purposes. In such cases, it is important to try to distinguish between "reactions" and "events", not only for administrative purposes but also to minimize the instances of reporting adverse events that are clearly unrelated to therapy. MAHs should help investigators understand their role in assessing the possible relationship between an adverse event and the administration of a health product during post-marketing studies.

Comparator and concomitant products used in these studies are within the scope of this guidance document. It is the sponsor's responsibility to decide whether active comparator and concomitant product adverse reactions should be reported to the MAH of the active control and/or directly to MHPD.

It should be noted that a domestic clinical trial AR report for a marketed product used for the purpose of a MAH-sponsored Phase I-III clinical trial in Canada is subject to Division 5 of the *Food and Drug Regulations*, and must be reported to the appropriate clinical division (e.g. Therapeutic Products Directorate, or Biologics and Genetic Therapies Directorate). Sponsors reporting adverse reactions to an appropriate clinical division of Health Canada in accordance with Division 5 of the *Food and Drug Regulations* or Part 4 of the *Natural Health Products Regulations* should not report those ARs to MHPD in duplicate. Please refer to Appendix 5 for information on the relevant clinical divisions.

4.2.2.2 Non-Market Authorization Holder Sponsored Studies

A MAH may receive study AR reports where its product was a comparator treatment (and therefore used in accordance with approved labelling) or was a product the patient was taking concomitant to the study medication but was suspected of causing an AR. The source of these reports may be another MAH who is sponsoring the study, a private investigator or an academic centre. The MAH must apply all principles outlined in this guidance document and the Regulations pertaining to reporting requirements, including determination of seriousness, causality, and minimal criteria for submitting an AR report. The MAH should not alter the causality assessment of the trial product(s) provided by the trial sponsor and should include any narrative of the trial sponsor regarding causality, if available. The MAH should assess causality on its own marketed health product(s).

4.2.2.3 Post-Study Adverse Reactions

Although such information is not routinely sought or collected by the sponsor, serious adverse reactions that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by an investigator to the sponsor. Such cases should be

regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment is needed for a decision on whether or not expedited reporting is required.

4.2.3 Blinded Study Reports (in Phase IV)

If the MAH receives a serious domestic AR report or a serious unexpected foreign AR report from the investigator that is blinded to individual patient treatment, the code must be broken before submitting the report to MHPD. Although it is advantageous to retain the blind for all patients prior to final study analysis, it is recommended that, when a serious AR occurs, the MAH seek a third party to break the blind only for that specific patient, even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for individuals such as biometrics personnel, who are responsible for analysis and interpretation of results at the conclusion of the study.

4.3 Regulatory Authority Sources

Individual serious unexpected AR reports originating from Canadian and foreign regulatory authorities are subject to expedited reporting to Health Canada by each MAH. If the product source, brand, or trade name is not specified, the MAH should assume that it was its own product, although the report should indicate that the specific brand was not identified.

As part of their surveillance activities, MAHs should consult the Canada Vigilance Adverse Reaction Online Database to identify reports for their products that were sent directly to the Canada Vigilance Program. If a MAH becomes aware of a report that has been submitted by a health professional or consumer to the Canada Vigilance Program, the MAH must also submit the report to the Canada Vigilance Program. In order to assist the Program with the identification of duplicates, please indicate the source of the report including Canada Vigilance as the source and quote the Canada Vigilance Adverse Event Report (AER) number. If additional information is required (e.g. complete case narratives), the MAH may request copies of AR reports through the Access to Information and Privacy Division of Health Canada and will require payment of the applicable fee.

Appendix 1 Glossary: Definitions and Terminology

Adverse Event[8] **(AE)**
An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

Adverse reaction (AR)
For the purpose of this guidance document means a noxious and unintended response to a marketed health product covered by this document and includes "adverse drug reaction" as defined in the *Food and Drug Regulations* and "adverse reaction" as defined in the *Natural Health Products Regulations*.

> "Adverse Drug Reaction"
> Adverse drug reaction as defined in the *Food and Drug Regulations* is a noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function.
>
> "Adverse Reaction"
> Adverse reaction as defined in the *Natural Health Products Regulations* is a noxious and unintended response to a natural health product that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function.

Brand Name (*Food and Drug Regulations*)
With reference to a drug, the name, whether or not including the name of any manufacturer, corporation, partnership or individual, in English or French,
(a) that is assigned to the drug by its manufacturer,
(b) under which the drug is sold or advertised, and
(c) that is used to distinguish the drug.

Brand Name (*Natural Health Products Regulations*)
Means a name in English or French, whether or not it includes the name of a manufacturer, corporation, partnership or individual
(a) that is used to distinguish the natural health product; and
(b) under which a natural health product is sold or advertised.

Canada Vigilance Program
Health Canada's Canada Vigilance Program is responsible for the collection and assessment of adverse reaction reports related to the following marketed health products: pharmaceuticals, biologics (including fractionated blood products and vaccines), natural health products, radiopharmaceuticals and cells, tissues and organs. The program is operated by the Marketed Health Products Directorate.

Common Name (*Food and Drug Regulations*)
With reference to a drug, the name in English or French by which the drug is
(a) commonly known, and
(b) designated in scientific or technical journals, other than the publications referred to in Schedule B to the Act.

Common Name (Natural Health Products)
For any medicinal or non-medicinal ingredient contained in a natural health product, the name by which it is commonly known and is designated in a scientific or technical reference.

Domestic AR
Adverse reaction occurring in Canada.

Drug
According to the *Food and Drugs Act*, a drug includes any substance or mixture of substances manufactured, sold or represented for use in:

a. the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
b. restoring, correcting or modifying organic functions in human beings or animals, or
c. disinfection in premises in which food is manufactured, prepared or kept.

Expected AR
An AR whose nature (i.e., specificity or outcome), severity or frequency is consistent with the terms or description used in the product labelling should be considered expected.

Expedited AR Report
The following must be reported by the MAH within 15 calendar days of receiving information:

- any serious domestic AR,
- any serious unexpected foreign AR, and
- any domestic unusual failure in efficacy for a new drug.

Foreign AR
An adverse reaction occurring outside Canada to a product with the same combination of active ingredients that is marketed in Canada irrespective of variations in the formulation, dosage form, strength, route of administration, or indication.

Health product
For the purpose of this guidance document, health products include the following products regulated under the *Food and Drug Regulations* ("drugs") and the *Natural Health Products Regulations* ("natural health products"):

- pharmaceutical drugs (which includes prescription and non-prescription pharmaceutical drugs);
- biologics as set out in Schedule D of the *Food and Drugs Act* (which include biotechnology products, vaccines and fractionated blood products);
- radiopharmaceutical drugs listed in Schedule C of the *Food and Drugs Act*; and
- natural health products as defined in Section 1 of the *Natural Health Products Regulations*.
- disinfectants as defined in Schedule C of the *Food and Drug Regulations*.

Individual Case[13]
An Individual Case is an adverse reaction report, the information provided by a primary source to describe most completely suspected adverse reaction(s) to the use of one or more health products by an individual patient at a particular point in time.

Individual Case Safety Report (ICSR)[12]
An ICSR is an Individual Case transmitted electronically.

Market authorization holder (MAH)
For the purpose of this guidance document means the entity that holds the Notice of Compliance, the Drug Identification Number (DIN), the Natural Product Number (NPN), the Homeopathic Medicine Number (DIN-HM), or the product licence.

Natural Health Product (NHP)
A substance set out in Schedule 1 of the *Natural Health Products Regulations* or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1 of the *Natural Health Products Regulations*, a homeopathic medicine or a traditional medicine, that is manufactured, sold or represented for use in

a. the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
b. restoring or correcting organic functions in humans; or
c. modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

However, a natural health product does not include a substance set out in Schedule 2 of the *Natural Health Products Regulations*, any combination of substances that includes a substance set out in Schedule 2 of the *Natural Health Products Regulations* or a homeopathic medicine or a traditional medicine that is or includes a substance set out in Schedule 2 of the *Natural Health Products Regulations*.

New Drug
As per the *Food and Drugs Regulations:* Division 8 (C.08.001):

a. a drug that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug;
b. a drug that is a combination or two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug; or
c. a drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug.

Product Monograph[19] **(PM)**
A product monograph is a factual, scientific document on the drug product that, devoid of promotional material, describes the properties, claims, indications, and conditions of use for the drug, and that contains any other information that may be required for optimal, safe, and effective use of the drug.

Phase IV Study[20] (Drugs)
All studies performed after the drug has been approved by the regulator for the market, and related to the approved indication. These studies are often important for optimizing the drug's use. They may be of any type but must have valid scientific objectives. Commonly conducted studies include safety studies designed to support use under the approved indication such as mortality and morbidity studies, or epidemiological studies.

Phase IV Study[21] (Natural Health Products)
All studies performed after the NHP has been approved by the regulator for the market and related to the approved conditions of use. These studies are often important for optimizing the NHP's use. They may be of any type but must have valid scientific objectives. Commonly conducted studies include safety studies and studies designed to support use under the approved conditions of use, such as mortality and morbidity studies or epidemiological studies.

Qualified Health Professional
A person who is a member in good standing of a professional medical, nursing, pharmacists' or other health care practitioner association and entitled to provide health care under the laws of the jurisdiction in which the person is located, or other individuals retained by the MAH who have the appropriate health care education and therapeutic expertise.

Registry[13]
An organized collection of data on humans within a particular disease, group or other special group (e.g., cancer, pregnancy, birth-defect, organ transplant, and serious skin disease registries).

Sell[18]
Includes offer for sale, expose for sale, have in possession for sale and distribute, whether or not the distribution is made for consideration.

Serious Adverse Reaction
For the purpose of this guidance document means a noxious and unintended response to a marketed health product covered by this document that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death and includes "serious adverse drug reaction" as defined in the *Food and Drug Regulations* and "serious adverse reaction" as defined in the *Natural Health Products Regulations.*

> "Serious Adverse Drug Reaction"
> A serious adverse drug reaction as defined in the *Food and Drug Regulations* is a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.
>
> "Serious Adverse Reaction"
> A serious adverse reaction as defined in the *Natural Health Products Regulations* is a noxious and unintended response to a natural health product that occurs at any dose and that requires in-patient hospitalization or a prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death.

Serious Unexpected Adverse Drug Reaction (*Food and Drug Regulations*)
A serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the drug.

Serious Unexpected Adverse Reaction (*Natural Health Products Regulations*)
A serious adverse reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the natural health product.

Solicited Report[8]

Solicited reports are those derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or health care providers, or information gathering on efficacy or patient compliance. Adverse event reports obtained from any of these should not be considered spontaneous.

Spontaneous Report

A spontaneous report is an unsolicited communication by a health professional or consumer to a company, regulatory authority or other organization (e.g., WHO, Regional Centre, Poison Control Centre) that describes one or more adverse reactions in a patient who was given one or more medicinal products* and that does not derive from a study or any organized data collection scheme.

*As extracted from ICH E2D. For the purposes of this guidance document, a medicinal product is a health product.

Stimulated Report

A report that may have been motivated, prompted or induced, such as advisories, literature report, publication in the press, or questioning of health professionals by MAH representatives. These reports should be considered unsolicited in nature.

Trading Partner[12]

An organization exchanging Electronic Data Interchange (EDI) messages in the area of pharmacovigilance in the pre- and post- authorization phase.

Unsolicited Report

See Spontaneous Report.

Appendix 2 References

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2. *Food and Drug Regulations*, Part C, Division 8, C.R.C., c. 870.
http://laws.justice.gc.ca/eng/regulations/c.r.c._c._870/index.html

3. *Natural Health Products Regulations*, Section 24, Reaction Reporting, C.R.C., SOR/2003-196.
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4. *Food and Drug Regulations*, Part C, Division 5, C. R. C., c.870.
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Appendix 3 Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AER	Adverse Reaction Report Number
AR	Adverse Reaction
ASR	Annual Summary Report
ATI	Access to Information
BGTD	Biologics and Genetic Therapies Directorate
CAMR	Canada's Access to Medicines Regime
CIOMS	Council for International Organizations of Medical Sciences
CTA	Clinical Trial Application
CTO	Cells, Tissues, and Organs
DIN	Drug Identification Number
DIN-HM	Homeopathic Medicinal Number
EDI	Electronic Data Interchange
FDR	*Food and Drugs Regulations*
GVP	Good Pharmacovigilance Practices
HC	Health Canada
HPC	Health Professional Communication
HPFB	Health Products and Food Branch
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
INN	International Nonproprietary Name

MAH	Market Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHPD	Marketed Health Products Directorate
NHP	Natural Health Product
NNHPD	Natural and Non-prescription Health Products Directorate
NHPR	*Natural Health Products Regulations*
PC	Public Communication
PM	Product Monograph
TPD	Therapeutic Products Directorate
TPMO	Trading Partner Management Office
The Regulations	Collectively, the *Food and Drug Regulations* and the *Natural Health Products Regulations*
WHO	World Health Organization

Appendix 4 Contact Information

Electronic Reporting – Trading Partner Management Office (TPMO)
The preferred method of reporting ARs is electronically. The TPMO provides a single point of contact for trading partners already enrolled with Canada Vigilance Program to submit ARs electronically as well as for MAHs seeking enrolment. For the guidance document on e-reporting, contact TPMO.

During normal business hours, the TPMO may be reached at:

HPFB Trading Partner Management Office
Health Canada
250 Lanark Avenue
Address Locator 2004D
Ottawa, Ontario
K1A 0K9
E-mail: tpmo_bgpc@hc-sc.gc.ca

Non-Electronic Reporting
For MAHs who are not yet enrolled as a trading partner, AR reports for marketed health products covered by this guidance document should be sent to:

Canada Vigilance Program
Health Canada
Address Locator 1908C
200 Eglantine Driveway
Ottawa, Ontario
K1A 0K9

Telephone: 613-957-0337
Facsimile: 613-957-0335
E-mail: CanadaVigilance@hc-sc.gc.ca **(DO NOT SEND REPORTS VIA E-MAIL)**

Access to Information
For copies of AR reports, consult the Access to Information website at:
https://www.canada.ca/en/treasury-board-secretariat/topics/access-information-privacy.html

Council for International Organizations of Medical Sciences (CIOMS)

CIOMS publications may be obtained directly from:

Council for International Organizations of Medical Sciences (CIOMS)
Case postale 2100
CH-1211 Geneva 2
Switzerland
Telephone: + 41 22 791 6497
Email: info@cioms.ch
Website: www.cioms.ch

International Council on Harmonisation (ICH)

ICH guidance documents may be obtained from:

ICH Secretariat
c/o IFPMA
9, chemin des Mines
1202 Geneva
Switzerland
Telephone: +41 22 338 3207
Email: admin@ich.org
Website: http://www.ich.org

Appendix 5 Other Adverse Reaction Reporting Programs Outside the Scope of this Document

Canada Vigilance Program and its partners collect adverse reaction reports in order to monitor health and safety risks related to the sale and use of a variety of products. In order to avoid delays in reporting, it is important to direct adverse reaction reports to the appropriate program area of expertise.

Refer to the following link which provides further information on adverse reaction reporting specific to other products that are not within the scope of this guidance document. All adverse reaction reports related to marketed health products should be sent to the Canada Vigilance national office (see Appendix 4).

Adverse Reaction Reporting for Specific Products:
https://www.canada.ca/en/health-canada/news/media-room/advisories-warnings/adverse-reaction-reporting.html

Appendix 6 World Health Organization Causality Algorithm

Refer to the following link for additional information on the WHO and the Centre for International Drug Monitoring (Uppsala Monitoring Centre): https://who-umc.org/

Causality Assessment of Suspected Adverse Reactions developed by the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden.

Term	Description	Comments
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.	It is recognized that this stringent definition will lead to very few reports meeting the criteria, but this is useful because of the special value of such reports. It is considered that time relationships between drug administration and the onset and course of the adverse event are important in causality analysis. So also is the consideration of confounding features, but due weight must placed on the known pharmacological and other characteristics of the drug product being considered. Sometimes the clinical phenomena described will also be sufficiently specific to allow a confident causality assessment in the absence of confounding features and with appropriate time relationships, e.g. penicillin anaphylaxis.
Probable / Likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.	This definition has less stringent wording than for "certain" and does not necessitate prior knowledge of drug characteristics or clinical adverse reaction phenomena. As stated no rechallenge information is needed, but confounding drug administration underlying disease must be absent.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	This is the definition to be used when drug causality is one of other possible causes for the described clinical event.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.	This definition is intended to be used when the exclusion of drug causality of a clinical event seems most plausible.
Conditional /	A clinical event, including laboratory test	

Term	Description	Comments
Unclassified	abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.	
Unassessable / Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.	

Appendix 7 Summary of Expedited Post-Market AR Reporting Requirements to MHPD

Summary of Expedited Post-Market AR Reporting Requirements to MHPD

Type of Reactions	Drug and Natural Health Product ARs to be Reported to MHPD Within 15 Calendar Days
Domestic Reports	
Unsolicited:	
Serious Unexpected	YES
Serious Expected	YES
Non-Serious Unexpected	NO
Non-Serious Expected	NO
Solicited (e.g., Studies*)	
Serious Unexpected	YES
Serious Expected	YES
Non-Serious Unexpected	NO
Non-Serious Expected	NO
Foreign Reports	
Unsolicited:	
Serious Unexpected	YES
Serious Expected	NO
Non-Serious Unexpected	NO
Non-Serious Expected	NO
Solicited (e.g., Studies*)	
Serious Unexpected	YES
Serious Expected	NO
Non-Serious Unexpected	NO
Non-Serious Expected	NO

*Studies not subject to clinical trial applications (CTAs)